UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title: **A PHASE 1 STUDY OF INO-A002 IN HEALTHY DENGUE VIRUS-NAÏVE ADULTS**

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*** Ask for the Immunodeficiency Program doctor on call**

Why am I being asked to volunteer?

You are being invited to participate in a research study of a product called INO-0002 for the prevention of infection from the Zika virus. This study is a clinical research trial to find out whether an investigational (not approved by the US Food and Drug Administration (FDA)) product is safe, tolerated, and can cause enough antibodies in your blood that may indicate the ability to prevent infection with Zika virus.

Zika virus infection is a disease that was relatively unknown prior to 2014. Zika virus was discovered in Africa and in 2015 spread into and across South America, Central America, and the Caribbean. Zika has been linked to congenital malformations in newborns of mothers who are infected during pregnancy, causing conditions such as microcephaly (small head and brains), retinal calcifications, and blindness. Zika can also cause a condition of a temporary paralyzing illness called Guillain Barré syndrome (GBS).

At present, there are no therapies that have been approved in humans to treat or prevent Zika virus infection. Some vaccines and a few drugs have been tested in studies but none has proven efficacious in preventing the infection.

The product that will be used in this study is different from vaccines because it doesn't need your immune system to respond to the shot. Vaccines inject a protein, or an inactivated virus and your immune system creates antibodies and other responses against what was injected.

With this product we will directly inject DNA into your muscle with the genetic information necessary for your muscle cells to make the antibody directly.

Vaccines are medicines given to make your immune system create resistance or immunity against a disease. INO-A002 used in this study for the first time in humans is a new way to provide protection against a virus infection because your body's immune system isn't needed for INO-A002 to make antibodies against the Zika virus. INO-A002 contains DNA that codes for an antibody against the Zika virus. The DNA included in INO-A002 was made in a laboratory, and was not made from Zika virus nor was Zika virus used to generate the DNA. The DNA is entirely synthetic – meaning it can be thought of as having been made in a test tube. There is no risk of getting Zika virus infection from INO-A002.

The Study Team will monitor the safety, side effects, and the antibody levels produced by INO-A002. INO-A002 will be given with an investigational device (called CELLECTRA®) that will deliver a small electric charge through 5 needles. This is called electroporation and is used to increase the amount of INO-A002 taken up by your muscle cells. This investigational device has also not been approved by the U.S. Food and Drug Administration (FDA) for use in this country but has been used in over 25 clinical studies like this one.

Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

The doctor in charge of this study at this site is Dr. Pablo Tebas. INO-A002 was developed by Dr. David Weiner, a researcher at the Wistar Institute. The study was designed by Dr. Pablo Tebas in collaboration with researchers at Inovio Pharmaceuticals. Dr. Pablo Tebas from University of Pennsylvania is the Principal Investigator overseeing the entire study. Funding for this research study comes from The Bill and Melinda Gates Foundation.

What is the purpose of this research study?

The purpose of this study is to evaluate the safety of dMAb-ZK190 and to help determine which dose of INO-A002 should be used in future studies to test in those who are at risk for Zika virus infection.

How long will I be in the study? How many other people will be in the study?

A total of approximately 24 subjects will be included in this study at 1 study location in the US (the University of Pennsylvania). The length of your participation in the study will be about 1 yearand will include 15 study visits.

What am I being asked to do?

Pre-entry screening: Before you can start the study, the study doctor or study staff with talk to you about the study. Then you will have to read and sign this consent form before the study doctor or study staff can begin the screening period. These screening procedures will be performed to determine if you are eligible to participate in this study. These procedures include:

Health and medication questionnaire: You will answer questions about your health, your medical history, and the medications you take. You will also be asked specific questions about infections in the past and travel history at any time in the past (see protocol Schedule of Events).

Physical Assessment: The study doctor will do a physical exam.

Weight and Height: Study staff will see how much you weigh and how tall you are.

Vital signs: Study staff will check your blood pressure, your pulse, listen to you breathe in and out, and take your temperature. **Electrocardiograms (ECGs):** Study staff will attach leads (electrical sensing devices) to your chest to measure the electrical activity of your heart.

Collect blood for safety testing of your blood counts, chemistry, liver and kidney functions, antibody testing for Human Immunodeficiency Virus (HIV, the virus that causes AIDS), hepatitis B and C (viruses that affect the liver), and mosquito borne viruses (dengue).

Pregnancy testing (blood) on women who are able to have children.

You will be permitted to enter the study if you meet the study criteria and if study related test results are satisfactory which will be decided by the study investigator.

YOU MUST TELL THE MEDICAL STAFF ALL ABOUT YOUR PREVIOUS AND CURRENT MEDICAL CONDITIONS AND ANY DRUGS (LEGAL AND ILLEGAL) OR HEALTH SUPPLEMENTS YOU ARE TAKING. FAILURE TO DO SO MAY PUT YOUR HEALTH AT RISK.

If you qualify to be in this study, you will be assigned to receive INO-A002 on day 0 for the first two groups and on day -3 and 0 for the last two groups at one of the following four doses given with the investigational CELLECTRA® device:

Cohort	Schedule	No. injections per dose	Dose (mg)
A	Day 0	1	0.5
B	Day 0	1	1
C	Day -3, 0	1+1	2
D	Day -3, 0	2+2	4

At day -3 or Day 0 of study (dose #1 depending on the groups you are assigned to): you will be asked about changes in your health since the last visit, have a physical examination, have your blood collected for monitoring lab tests, and have a urine pregnancy test if you are a woman who can become pregnant. You will receive your first dosing (1 or 2 injections, depending on which dosing group you have been assigned to) and electroporation (electroporation procedure is described below). You will stay in the Clinical Trials Research Center for a minimum of half an hour to be monitored closely for any side effects. You will be given a checklist to take home and write down any symptoms or reactions that you notice.

Day 1, 3, 7 and every week for 8 weeks and then monthly at months 3, 4, 5 ,6 and 12: you will return for a brief physical exam (if needed), and to give blood samples to monitor the safety of dMAb-ZK190 and the antibody levels in your blood. You will discuss your checklist with the study staff.

Between 20 and 30 ml (2-3 tablespoons) of blood and urine will be taken at most of the study visits. The screening visit will require, between 3 and 5 tablespoons. The total blood collected over the course of the study is approximately 400 ml (about 35 tablespoons).

You must agree not to engage in any high-risk behavior including intravenous drug use and unprotected sexual intercourse.

If for any reason you discontinue the study (and refuse to get more doses) you will be asked to continue the study visits, or at least come to our clinic to complete the final visit, which is exactly as the 6 month visit (see above).

CELLECTRA® Procedure:
This study procedure will occur with each administration of vaccine: at Day – 3 and 0. The study personnel will insert the needles from the investigational CELLECTRA® device into the muscle on your arm after injection of INO-A002. Then there will be 3 short pulses from the CELLECTRA® device lasting less than 1 second each. Your arm may move slightly as a result of the pulse delivered into the muscle. The investigational CELLECTRA® device will be used to get the study medication into the muscle cells. In addition, you may be offered Tylenol (acetaminophen) or Motrin (ibuprofen) to help with pain related to the injection. The study staff will help you decide which medications you need, if any.

Pain Evaluation:
Immediately after and at 5 and 10 minutes following each injection, you will rate the amount of discomfort you experienced during the injection

What are the possible risks or discomforts?

The experimental agent used in this study may have side effects, some of which are discussed below. Please note that these lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study vaccine side effects, please ask the medical staff at your site.

Risks of injections in the skin

- Injection site reactions such as redness, pain, swelling, bleeding, bruising, a warm

feeling, or in rare cases infection.
- Allergic reactions including itchy rash, hives, low blood pressure, sudden body swelling, breathing difficulty; in very rare cases, reactions can lead to death. Other immune reactions could occur such as serum sickness (fever, abdominal pain, diarrhea, joint pain and swelling). Therefore, clinic staff will watch you for a minimum of 30 minutes after each vaccination.

Risks of DNA Vaccines

More than 1200 people have received various DNA plasmid products other than those developed by Inovio and/or GeneOne and more than 1,300 individuals have received DNA plasmid products that are similar to INO-A002 developed by Inovio.

DNA plasmid products have been given to animals and humans without any problems being found but it cannot be certain that they will continue to be safe for humans. The possible risks related to DNA plasmid products - which are theoretical (a guess as to what could happen) and haven't been observed to date include: cell damage, antibodies to DNA, insertion of the DNA into the body's DNA, insertion of the DNA into bacteria leading to the formation of a new bacterium which might resist some antibiotics, or insertions of the DNA into a virus leading to formation of a new virus. None of these possible risks of DNA plasmid products has been seen in laboratory tests or in animals or humans so far.

Risks of INO-A002: INO-A002 is a DNA plasmid product. This particular vaccine has never been in humans, so we do not know the safety profile of this vaccine, so we will be evaluating side effects very carefully. People in other studies using injected DNA plasmid products have experienced minimal bleeding, bruising, redness and swelling at the injection site. There have been no bad effects on the kidneys, liver, heart, or other organs. We expect that the safety profile of this vaccine will be similar.

Risks of CELLECTRA®

Reactions observed in patients who have received DNA followed by the **CELLECTRA®** device are summarized below.

Common
- Mild to moderate administration site pain, redness, swelling, hardness at the injection site
- Not feeling well, tiredness, or headache in the first few days following immunization
- Visible lesion, scar and or/discoloration at the injection site

Less Common
- Injection site bruising, redness, laceration, other transient lesions, or bleeding related to the injection procedure
- Bruising, redness, or itching at near the administration site
- Joint pain or nausea

Uncommon or Rare
- Laceration, other transient lesions, or bleeding related to the injection procedure
- Severe administration site pain or tenderness
- Rash
- Lightheadedness/dizziness related to the injection/EP procedure

- Transient changes in clinical laboratory values such as CPK (muscle enzyme) or the aspartate transaminase (AST, also released from muscle)

Other possible side effects

Tylenol (acetaminophen): Rarely large doses or long term usage can cause liver damage, rash, itching, fever, lowered blood sugar. These side effects are unlikely at the doses being used for this study.

Motrin (ibuprofen): large doses or long-term usage can cause kidney damage.

Risks of blood drawing

Taking blood may cause discomfort, bleeding, or bruising where the needle enters the body, and in rare cases, fainting or infection.

Other risks of being in this study

There may be risks or serious and/or life-threatening side effects when other medications or herbal supplements are taken with the study vaccine. For your safety, you must tell the study doctor or nurse about all medications you are taking besides the study vaccine before you start the study, and also before starting any new medications while on the study. In addition, you must tell the doctor or nurse before enrolling in any other clinical trials while on this study.

Unknown/Unforeseeable Risks and Discomforts

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. The research may involve risks that are currently unknown. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away. In some cases, side effects can be serious, long lasting, or may never go away.

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study medication, including severe or life-threatening allergic reactions or interactions with another medication. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Reproductive Risks

INO-A002 has unknown effects for unborn babies. You must agree not to become pregnant or make a woman pregnant.

Because of the risk involved, you and your partner must use an acceptable method of birth control that you discuss with the study staff. You must continue to use birth control until six months after you have received all vaccines. Acceptable birth control methods are listed below:

- Birth control drugs that prevent pregnancy given by pills, shots or placed under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. **If you think that you or your partner may**

have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility, and may request to track your pregnancy and will report the pregnancy to the Sponsor and the IRB. (An IRB is a committee responsible for making sure that the study follows the guidelines for the protection of human research subjects). You will not be allowed to breast-feed during this study. If you become pregnant, the health of your baby will be followed for a year after birth.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You may receive no benefit from being in this study. Information learned from this study may help those who are at risk for Zika virus infection.

What other choices do I have if I do not participate?

Instead of being in this study you have the choice of:
No participation in this study. Please talk to your doctor about this and other choices available to you. Your doctor will explain the risks and benefits of these choices.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected.

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), or the site's Institutional Review Board (IRB).
- The sponsor stops the study.
- You are not able to attend the study visits as required by the study**.**
- You become pregnant or begin breastfeeding.
- Continuing the study vaccinations may be harmful to you.
- You need a treatment that you may not take while on the study.
- You are not able to take the study vaccinations as required by the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

HIPAA AUTHORIZATION

The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania

Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What information about me may be collected and used or shared with others?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, email address
- Dates directly related to you such as date of birth and clinic visits.
- Personal and family medical history
- Current and past medications or therapies
- Questionnaires
- Results of tests and procedures you will undergo during this research
- Social Security Number, Medical record number

Why is my information being used?

Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. In some situations, your personal health information might be used to help guide your medical treatment.

Who may use or share information about me?

The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Other authorized personnel at Penn, including offices that support research operations.
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB.

Who, outside the School of Medicine, might receive my information?

As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

<u>Individuals or organizations responsible for administering the study:</u>

- Data for this study will be recorded on case report forms, keyed into a central database and electronically submitted to the Data Coordinating Center. The data will be cleaned and stored at this facility until it is ready to be analyzed.
- Approved data will be downloaded from the above mentioned Data Center for statistical analysis at the University of Pennsylvania. Specific study reports will be periodically provided to the study team and data safety review board to monitor if the trial is safe.
- Monitors from the University of Pennsylvania will visit the Clinical Trials Unit to review data and correct mistakes before the data are sent for analysis.

- Government Agencies: Data from this study will be made available to the Food and Drug Administration and to the Gates Foundation for them to evaluate the safety and efficacy of the treatments being used in this study.

In addition:

- If you test positive for HIV, hepatitis B or C, by law we have to report the infection to the City of Philadelphia Health Department/PA Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born. The purpose of reporting a positive HIV result is to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV.
- The electrical output, in other words information on the current, voltage and resistance during each electroporation of the CELLECTRA® device, will be reported to Inovio Pharmaceuticals who makes the CELLECTRA® to ensure that the device works properly. Additionally, data from the study will be discussed with the scientists involved with this study at the University of Pennsylvania; however, such data will NOT have any personally identifying information to be able to link any information to a study participant.

- Regulatory and safety oversight organizations
  The Office of Human Research Protections

  Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name, date of birth or medical record number. Information regarding your health, such as side effects of the study drug you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

  The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine be able to use or disclose your personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission

- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You must do so in writing to Dr. Pablo Tebas at Infectious Disease Division, 502 Johnson Pavilion Philadelphia PA 19104. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.
A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

What Are the Costs To Me?

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures.

Will I Receive Any Payment?

To compensate you for your time, transportation or other expenses you may incur as a participant you will receive $50 for the pre-entry screening visit, $150 dollars for each visit that has an injection (up to 2 visits), $50 for other visits including the final study visit. You will receive the compensation either by check or a reloadable pre-paid card called ClinCard *after* the visit has occurred. There are 15 total visits in the study that include up to 2 injection visits. Thus if you complete today's visit, all study visits, and the final visit, you will be compensated a total of $850 (for cohorts C and D only, $950) for the study. You will not be compensated for telephone contact for follow up.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the Gates Foundation. You will not be giving up any of your legal rights by signing this consent form.

What Are My Rights As a Research Subject?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I Have Questions Or Problems?

If you have questions about this study or a research-related injury, please contact the research team listed on page 1 of this consent form.

For questions about your rights as a research subject, contact:

- Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

STORAGE OF SAMPLES FOR FUTURE USE (OPTIONAL)

- As part of this clinical trial, your blood may be used for other studies to determine the best way to diagnose Zika virus infection. If additionally studies of the immunity generated against Zika virus are considered useful, the researchers would like to be able to use blood and serum that are left over from the blood draws during the study. Blood will be stored at Quest Diagnostics Research Division with all samples identified by a code but without any identifying information. Identifying information is stored separately by the study team but only has the Participant Identification Number. All

Protected Health Information (information which identifies you) is stored at the University of Pennsylvania by the study team. Samples will be stored for up to 5 years for additional studies and destroyed at that time.

- If at any time you change your mind about study participation or the storage of blood samples for future use, blood already collected and stored will be kept by the study team. If, however, you desire that any stored blood be destroyed and not kept, then please notify the study staff so that your blood can be removed from the storage facility.

- **Please indicate below whether you approve the use of your leftover blood**.

_____ YES _____ NO _____ Initials

CONSENT

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	_____
Name of Subject (Please Print)	Signature of Subject	Date
_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date/Time